IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

CHIESI, INC., CORNERSTONE BIOPHARMA, INC., and EKR THERAPEUTICS, LLC,	)	
Plaintiffs,	)	
v.	)	C.A. No. 13-cv-01275-GMS
EXELA PHARMA SCIENCES, LLC, EXELA PHARMASCI, INC., and EXELA HOLDINGS, INC.,	)	
Defendants.	)	

DEFENDANTS' OPENING CLAIM CONSTRUCTION BRIEF

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I. INTRODUCTION

This patent infringement action involves four patents relating to the drug product nicardipine hydrochloride for injection, which is used for the short-term treatment of hypertension. As shown in the parties' Joint Claim Construction Chart (D.I. 48-1, Ex. A), the parties agree that the Court should construe two claim terms which are common to the patents in suit: (1) "a pre-mixed aqueous solution" and (2) "buffer"/"buffer in an amount to maintain pH from about 3.6 to about 4.7."[1] Construction of these terms should be a straightforward process, because Exela's proposed constructions are taken directly from the claims, specifications and prosecution histories of the patents in suit.

For instance, the patents expressly define "pre-mixed" as "a composition [*i.e.*, aqueous solution] that does not require reconstitution or dilution before administration to a patient." (JA Ex. A, col. 3:10-12.) Exela proposes this unequivocal definition as the proper construction of the term because it is the definition chosen by the inventors. It also fits with the claim language, covers all the embodiments in the common specification of the patents, and conforms with the patentee's statements in the prosecution histories. The intrinsic evidence resolves this issue.

Likewise, Exela's proposed construction of "buffer" is compelled by the claims and common specification of the patents. Both the claims and the specification consistently identify the buffer as a ***separate and distinct*** component of the composition "***in addition*** to nicardipine and/or its pharmaceutically acceptable salts" and the other components that can be added to the composition. (*See id.* at col. 4:20-24 (emphasis added).) For example, Table 1 of the specification shows various embodiments of the purported invention, all of which add a separate

[1] Plaintiffs also assert that the phrases "one year at room temperature" and "three months at room temperature" require construction. (D.I. 48, Ex. A at 3-6.) Exela believes these phrases do not require construction. Exela will respond to Plaintiffs' position in Exela's responsive claim construction brief if necessary but does not discuss them herein.

and distinct buffer. (*Id.* at col. 8:1-27.) Moreover, the disclosed and claimed methods of making the compositions recite adding the ingredients necessary to form a distinct buffer. The patents further state that the separate and distinct buffer must have "***sufficient buffering capacity to maintain the desired pH range throughout the shelf-life of the product***." (*Id.* at col. 4:20-24 (emphasis added).) Again, the intrinsic evidence resolves the construction, and there is no need to go further.

For the reasons that follow, the Court should adopt Exela's claim constructions.

II. THE PATENTS IN SUIT AND THEIR PROSECUTION HISTORY

The patents in suit are U.S. Patent Nos. 7,612,102 ("the '102 Patent"), 7,659,290 ("the '290 Patent"), 7,659,291 ("the '291 Patent") and 8,455,524 ("the '524 Patent"). The patents in suit are all from the same family,[2] and they share identical specifications ("the common specification"). They describe and claim "pre-mixed" injectable pharmaceutical compositions (or formulations) containing nicardipine or a pharmaceutically acceptable salt thereof as the active pharmaceutical ingredient ("API"). (*See, e.g.*, JA Ex. A, col. 2:10-13, 3:7-10.[3]) Nicardipine is a "calcium ion influx inhibitor useful for the treatment of cardiovascular and cerebrovascular disorders." (*Id.* at col. 1:14-19.) Examples of the disorders treated by nicardipine disclosed in the specification include high blood pressure (*i.e.*, hypertension), angina, congestive heart failure and cerebral insufficiency. (*Id.* at col. 12:9-21.)

In addition to the nicardipine API, the claimed compositions can "further comprise" a tonicity agent "used to adjust the osmolality of the premixed pharmaceutical compositions to bring it closer to the osmotic pressure of body fluids, such as blood or plasma" (*Id.* at col. 5:42-

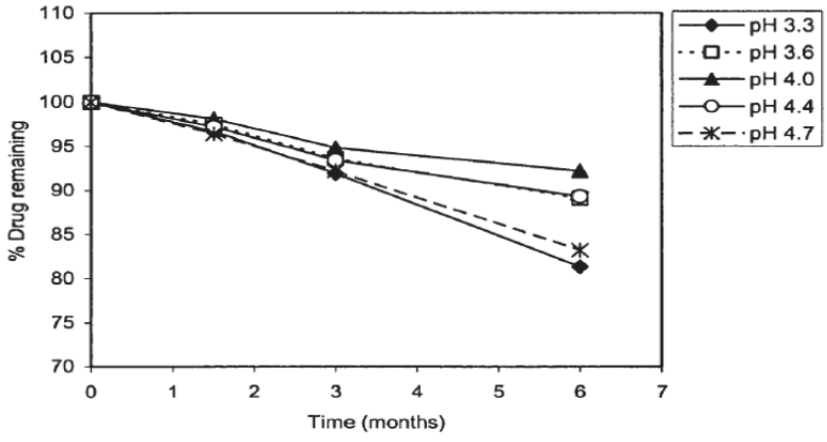
[2] The '290 and '291 Patents are divisional patents of the '102 Patent, and the '524 Patent is a continuation patent of the '291 Patent.

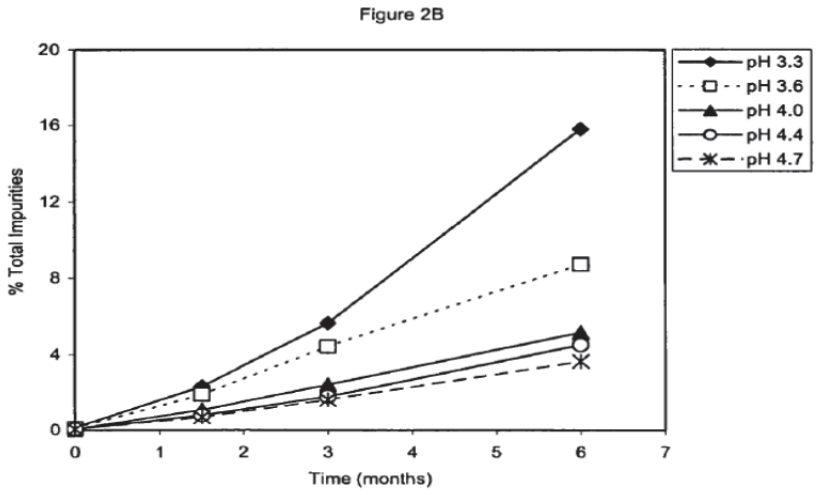
[3] For ease of reference, unless otherwise noted, Exela's citations are to the specification of the '102 Patent.

45.) They also can "further comprise" a "buffer" in an amount "to maintain the desired pH range throughout the shelf-life of the product." (*Id.* at col. 4:20-24.) Finally, the compositions can also "further comprise" a pH adjuster, which is added as needed to achieve a desired pH. (*Id.* at col. 5:22-26.) An "alternative aspect" of the purported invention can also include a cosolvent or a complexing agent in the composition with nicardipine hydrochloride and the buffer. (*Id.* at col. 11:13-17.)

The buffer is added to the claimed nicardipine compositions because according to the common specification proper "pH is important for the long term stability of nicardipine in the premixed pharmaceutical compositions." (*Id.* at col. 4:24-26.) Indeed, the specification describes the compositions as having a "buffered pH" that makes them "stable at room temperature for at least one year." (*Id.* at col. 1:64-67.) Based in part on the data shown below in Figures 2A (showing loss of the API from the composition over time) and 2B (showing total impurities in the composition over time), the patents in suit state that the desired pH range for the pre-mixed compositions is "about 3.6 to about 4.7." (*Id.* at col. 4:26-31, Figs. 2A-2B & 3A-3B.)

Figure 2A





Figures 2A and 2B of the Patents In Suit

Claim 1 of the ’102 Patent separately recites the components of the claimed pre-mixed pharmaceutical compositions:

> 1. A pharmaceutical composition for parenteral administration comprising a **pre-mixed aqueous solution** with a pH from about 3.6 to about 4.7 comprising:
>
> from about 0.1 to 0.4 mg/mL nicardipine hydrochloride;
>
> a tonicity agent selected from (i) about 4.5% to about 5% dextrose or (ii) about 0.8% to about 0.9% sodium chloride; and
>
> a **buffer** in an amount to maintain pH from about 3.6 to about 4.7;
>
> the aqueous solution contained in a pharmaceutically acceptable container such that the solution does not come into contact with polar polymers;
>
> the aqueous solution when stored in the container for at least one year at room temperature exhibiting (i) less than a 10% decrease in the concentration of nicardipine hydrochloride and (ii) a total impurity formation of less than about 3%.

(*Id.* at col. 27:59-28:28 (emphasis added).) The '290 Patent in turn claims methods of making such pre-mixed pharmaceutical compositions (JA Ex. B, col. 27:28-28:49), while the '291 and '524 Patents claim methods of treating acute elevations of blood pressure or inducing hypotension using such compositions (JA Ex. C, col. 27:15-28:53; JA Ex. D, col. 27:59-30:39).

During prosecution of the application that led to the '102 Patent, the applicants relied on the fact that the claimed composition was "pre-mixed" to overcome an obviousness rejection. (JA Ex. F at A-134; JA Ex. G at A-143.) The prior art contained nicardipine hydrochloride compositions available in a concentrated form packaged in glass ampules. (JA Ex. G at A-142.) The Examiner's summary of an examiner interview indicates the applicants asserted that the premixed formulation claimed was "not the same as" the concentrated form of nicardipine. (JA Ex. F at A-134.) In response to a pending office action, the applicants argued that "the concentrated ampule formulations of nicardipine hydrochloride present a number of issues for patients and health care professionals," including delayed administration due to the time needed to dilute and reconstitute the ampule formulation and potential dosing errors. (JA Ex. G at A-142.) The applicant alleged that the claimed invention resolved these issues because it was "ready-to-use." (*Id.* at A-143.) Subsequent to this representation, the PTO issued a Notice of Allowability, and the Examiner stated the reason for allowance was "Applicant submitted declarations under 37 C.F.R. § 1.132 (07/06/2009) presenting evidence for the advantageous stable form of a low concentration drug only with the particular combination of dextrose or sodium chlorides, ***a buffer to maintain pH from about 3.6 to about 4.7*** and storage in a non polar bag." (JA Ex. J at A-188 (emphasis added).)

III. THE LAW OF CLAIM CONSTRUCTION

Claim construction is an issue of law. *See Markman v. Westview Instruments, Inc*., 517 U.S. 370, 372 (1996). Claim terms "are generally given their ordinary and customary meaning . . . [which] is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e., as of the effective filing date of the patent application." *Phillips v. AWH Corp*., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (internal quotation omitted). To determine how the skilled person would have understood disputed claim language, courts look to the words of the claims themselves, the patent specification, and the prosecution history. *Id.* at 1314. A "person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id*. at 1313. The "ordinary meaning" of a claim term is therefore its meaning to one of ordinary skill after reading the entire patent. *Netcraft Corp. v. eBay, Inc*., 549 F.3d 1394, 1397 (Fed. Cir. 2008) (quoting *Phillips*, 415 F.3d at 1321).

The intrinsic record is the best source to use to understand the patent claims and is usually dispositive of the proper claim construction. *Phillips*, 415 F.3d at 1316-17; *C.R. Bard, Inc. v. U.S. Surgical Corp*., 388 F.3d 858, 861 (Fed. Cir. 2004). Intrinsic evidence consists of "the patent itself, including the claims, the specification and, if in evidence, the prosecution history." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The specification "is the single best guide to the meaning of a disputed term." *Id.* Claim terms can be defined only in ways that are consistent with the specification. *Phillips*, 415 F.3d at 1316 (citing *Markman*, 517 U.S. at 389); *Merck & Co., Inc. v. Teva Pharms. USA, Inc*., 347 F.3d 1367, 1371 (Fed. Cir. 2003).

Indeed, a patentee is entitled to be his or her own lexicographer by defining a term in the specification of a patent. *See Sinorgchem Co. v. Int'l Trade Comm'n,* 511 F.3d 1132, 1136-38 (Fed. Cir. 2007) (holding that the patentee was bound by an express definition of a claim term in the specification). When the specification defines a term, that definition governs. *Id.*; *Jack Guttman, Inc. v. Kopykake Enters., Inc.*, 302 F.3d 1352, 1360-61 (Fed. Cir. 2002). However, while claims must be construed in light of the specification, the specification cannot be used to rewrite the claims. *Phillips*, 415 F.3d at 1323. Courts should not import limitations from the specification into otherwise unambiguous claim terms. *Id.*

IV. ARGUMENT

A. "Pre-Mixed Aqueous Solution"

1. The patents expressly define the claimed "pre-mixed aqueous solution."

The term "pre-mixed aqueous solution" should be construed in accordance with Exela's proposed construction:

Claim Term	Exela's Proposed Construction	Plaintiffs' Proposed Construction
"Pre-Mixed Aqueous Solution"	An aqueous solution that does not require reconstitution or dilution before administration to a patient.	A ready-to-use pharmaceutical composition that is an aqueous solution already mixed from the point of manufacture and is stable, allows medical personnel to use prepared containers containing an injectable formulation off the shelf without additional preparation, avoids potential contamination problems, and eliminates dosage errors.

The common specification provides an express definition of the term "pre-mixed": "As used herein, the term 'pre-mixed' refers to a pharmaceutical composition that does not require reconstitution or dilution before administration to a patient." (JA Ex. A, col. 3:10-12; *see also*

id. at col. 2:20-22 ("The pharmaceutical compositions described herein require no dilution prior to administration . . . .").) It therefore logically follows that a "pre-mixed aqueous solution" is "an aqueous solution that does not require reconstitution or dilution before administration to a patient." Simply put, the patentee acted as its own lexicographer in defining this term. *See Sinorgchem*, 511 F.3d at 1136 (holding that a specification's use of quotation marks around a term followed by an explanation of what the term means is a "strong indication" of a definition, and the patentee is bound by that definition).

This express definition of "pre-mixed" as a "pharmaceutical composition that does not require reconstitution or dilution before administration to a patient" is supported by the distinctions the common specification draws between the prior art ampule compositions and the claimed pharmaceutical compositions. The specification contrasts the disclosed "pre-mixed" compositions with the prior art ampule formulations that require dilution prior to being administered to a patient. (JA Ex. A, col. 3:10-19.) In fact, the "pre-mixed" compositions are alleged to be superior to the ampule formulation specifically because they do not require dilution prior to administration to a patient. (*Id.*) Dilution of the ampule formulation prior to administration to a patient can be difficult in emergency situations and introduces the potential for instability, variable pH, dosage errors, contamination, and the creation of medical waste. (*Id.* at col. 1:39-57; *see also id.* at col. 2:4-9, Fig. 1.)

2. The prosecution history supports the common specification's express definition of "pre-mixed."

During prosecution, the patentee distinguished between the claimed compositions and the prior art nicardipine ampule. The patentee described the prior art as being directed toward *concentrated* nicardipine which was "not the same as the premixed formulation presented in the claims." (JA Ex. F at A-134.) By implication, the compositions in the claims are not

"concentrated." The term "concentrated" on its face suggests dilution is necessary prior to use. Because the claimed compositions at issue are not concentrated, they do not require dilution.

The applicant also argued for patentability, and submitted supporting expert testimony, by pointing out the supposed drawbacks of the prior art which the "pre-mixed" compositions allegedly overcome. Both the argument and the supporting declaration draw attention to the fact that the concentrated formulation in the prior art ampules require dilution or reconstitution prior to administration to a patient. (JA Ex. G at A-142; JA Ex. H at ¶¶ 6, 10.) That is, the patentee distinguished the claimed compositions from the prior art on the basis that the claimed compositions do not require dilution like the prior art and thus avoids the art's purported shortcomings. (JA Ex. G at A-142-43; JA Ex. H at ¶¶ 11-12.) This point of distinction further demonstrates that a "pre-mixed aqueous solution" is one that does not require reconstitution or dilution prior to administration to a patient.

3. Plaintiffs' construction of "pre-mixed aqueous solution" is unduly narrow.

Plaintiffs' proposed construction of "pre-mixed aqueous solution" improperly adds multiple narrowing limitations that are cobbled together from unrelated portions of the specification. (D.I. 48-1, Ex. A at 1.) For example, Plaintiffs' look to an alternative, narrower definition of the term "pre-mixed" that relates to an alternative embodiment not at issue in this case to argue that the solution has to be pre-mixed "from the point of manufacture." (*Id.*) Plaintiffs also read in limitations about "additional preparation," "potential contamination problems," and "dosage errors." (*Id.*) Such narrowing limitations should not be read into the claim language where, as discussed above in Sections IV.A.1-IV.A.2, the specification and prosecution history disclose a broader definition of the term. *Superguide Corp. v. DirecTV Enters., Inc.*, 358 F.3d 870, 875 (Fed. Cir. 2004 ("[A] particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the

embodiment."). Plaintiffs' narrowing construction should be rejected by the Court, and Exela's proposed construction based on the intrinsic evidence should be adopted.

B. The "Buffer" Limitations

The term "buffer" and the phrase "buffer in an amount to maintain pH from about 3.6 to about 4.7" should be construed as proposed by Exela.[4] In each of Exela's constructions, the buffer must (1) be "separate and distinct" from the other components of the composition and (2) have sufficient buffering capacity to maintain the optimal pH range of the composition:

Claim Term or Phrase	Exela's Proposed Construction	Plaintiffs' Proposed Construction
"Buffer"	Component of the composition (or aqueous solution) separate and distinct from nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster that has sufficient buffering capacity to maintain an optimal pH range throughout the shelf-life of the product.	A system capable of maintaining the pH within an optimal pH range.
"Buffer In An Amount To Maintain pH From About 3.6 To About 4.7"	Component of the composition (or aqueous solution) separate and distinct from nicardipine hydrochloride, tonicity agent, cosolvent, water and/or pH adjuster that has sufficient buffering capacity to maintain a pH range from about 3.6 to about 4.7 throughout the shelf-life of the product.	A system capable of maintaining the pH within an optimal pH range in an amount to maintain the pH from about 3.6 to about 4.7.

1. The claim language demonstrates that the "buffer" is separate and distinct.

The claim structure requires that the claimed buffer is a separate and distinct component from the other components of the composition (or aqueous solution). As shown in Section II

[4] By way of example, the term "buffer" is found in claim 1 of the '290 Patent (JA Ex. B, col. 27:27-43), while the phrase "buffer in an amount to maintain pH from about 3.6 to about 4.7" is found in claim 1 of the '102 Patent (JA Ex. A, col. 27:59-28:28).

above, claim 1 of the ’102 Patent separately requires (a) nicardipine hydrochloride, (b) a tonicity agent and (c) a buffer. (JA Ex. A, col. 27:59-28:28.) The same is true for all of the independent claims of the patents in suit—in each claim the buffer is set forth as a separate component. Even claim 11 of the ’290 Patent, which claims a method of making these pharmaceutical compositions, recites separately adding “citric acid” to the compositions to form a separate citrate buffer. (JA Ex. B, col. 28:32-49.) The claim’s structure alone thus mandates that the buffer is separately and distinctly present in the claimed compositions from the other listed ingredients. *Becton, Dickinson & Co. v. Tyco Healthcare Group*, 616 F.3d 1249, 1254 (Fed. Cir. 2010) (“Where a claim lists elements separately, the clear implication of the claim language is that those elements are distinct component[s] of the patented invention.” (internal quotation marks omitted)).

Moreover, the language of claim 1 of the ’102 Patent states that the buffer must be present in “an amount to maintain pH from about 3.6 to about 4.7.” (JA Ex. A, col. 27:59-28:28.) One of ordinary skill in the art, reviewing the common specification, would understand that the buffer must be a separate and distinct component added to a composition containing nicardipine hydrochloride in order to maintain this optimal pH range throughout the shelf-life of the product. (*See* discussion below in Section IV.B.2 concerning the pH levels in a nicardipine hydrochloride composition.)

2. <u>The common specification demonstrates that the “buffer” is separate and distinct.</u>

The common specification further supports the construction of the claimed buffer as a separate and distinct component of the claimed composition (or aqueous solution) that is added to maintain the optimal pH range throughout the shelf-life of the product. As discussed above, the common specification states that the compositions of the invention comprise nicardipine or

its salts, and may additionally comprise one or more of a buffer, a tonicity agent, and a pH adjuster. (JA Ex. A, col. 4:20-24, 5:22-25, 5:41-42.) With respect to the inclusion of a buffer, the specification states:

> In some embodiments, the premixed formulation comprises, ***in addition*** to nicardipine and/or its pharmaceutically acceptable salts, ***a buffer that has sufficient buffering capacity to maintain the desired pH range throughout the shelf-life of the product.*** As shown in FIGS. 2A and 2B, pH is important for the long term stability of nicardipine in the premixed pharmaceutical compositions. Although the pH of the premixed pharmaceutical compositions can range from between about 3.0 to about 7.0, pharmaceutical compositions having a pH within the range of about 3.6 to about 4.7 exhibit a lower percentage of drug degradation and total impurities (See FIGS. **2**A, **2**B, **3**A and **3**B).

(*Id.* at col. 4:20-31 (emphasis added); *see also id.* at col. 3:15-19 ("the premixed pharmaceutical compositions provided herein are stable at room temperature for 6 months or longer due to ***the inclusion of a buffer capable of maintaining the pH within an optimal pH range*** . . . .") (emphasis added).) Indeed, every embodiment of the nicardipine hydrochloride compositions disclosed in the patents in suit lists a buffer as a separately-added component from the nicardipine, tonicity agent, and other components, such as a pH adjuster. (*See, e.g., id.* at col. 2:10-13 ("The present disclosure relates to premixed pharmaceutical compositions comprising nicardipine or pharmaceutically acceptable salts thereof, one or more tonicity agents, and a buffer."), 7:65-8:25 (discussing embodiments in Table 1), 8:65-9:32 (disclosing four embodiments, each having a separately added buffer), 11:13-17 ("alternative aspect" of disclosed compositions still includes a buffer).)

Table 1 in the common specification demonstrates that the buffer is a separate and distinct component of the claimed compositions. Table 1 identifies eight "premixed pharmaceutical compositions comprising the active ingredient [nicardipine hydrochloride], a

tonicity agent, a buffer and optionally, a cosolvent . . . ." (*Id.* at col. 7:65-67.) Each of the embodiments in Table 1 identifies citric acid as the component used to make a buffer in the compositions:

TABLE 1

Active Ingredient	Tonicity Agent(s) (mg/ml)	Buffer (mg/ml)	Cosolvent (mg/ml)	pH
nicardipine hydrochloride (0.1 mg/ml)	NaCl (8.6 mg/ml)	Citric acid, anhydrous (0.0192 mg/ml)	Sorbitol (1.92 mg/ml)	3.6-4.7
nicardipine hydrochloride (0.1 mg/ml)	Dextrose, hydrous (48 mg/ml)	Citric acid, anhydrous (0.0192 mg/ml)	Sorbitol (1.92 mg/ml)	3.6-4.7
nicardipine hydrochloride (0.1 mg/ml)	NaCl (9 mg/ml)	Citric acid, anhydrous (0.0192 mg/ml)	None	3.6-4.7
nicardipine hydrochloride (0.1 mg/ml)	Dextrose, hydrous (50 mg/ml)	Citric acid, anhydrous (0.0192 mg/ml)	None	3.6-4.7
nicardipine hydrochloride (0.2 mg/ml)	NaCl (9 mg/ml)	Citric acid, anhydrous (0.0384 mg/ml)	None	3.6-4.7
nicardipine hydrochloride (0.2 mg/ml)	Dextrose, hydrous (50 mg/ml)	Citric acid, anhydrous (0.0384 mg/ml)	None	3.6-4.7
nicardipine hydrochloride (0.2 mg/ml)	NaCl (8.3 mg/ml)	Citric acid, anhydrous (0.0384 mg/ml)	Sorbitol (3.84 mg/ml)	3.6-4.7
nicardipine hydrochloride (0.2 mg/ml)	Dextrose, hydrous (46 mg/ml)	Citric acid, anhydrous (0.0384 mg/ml)	Sorbitol (3.84 mg/ml)	3.6-4.7

(*Id.* at col. 8:1-25.)

The reason a buffer is separately added to the claimed compositions is that the specification disclosed that nicardipine hydrochloride compositions need to be maintained within an optimal pH range to ensure they will be stable throughout the shelf-life of the product. Example 2 of the patents in suit, which references Figures 2A-2B and 3A-3B, discusses the results of studies conducted by the patentee on the "effect of pH on stability" of the claimed compositions. (*Id.* at col. 14:56-15:29.) "The results from this study indicate that the formulation pH has a significant effect on stability of a ready-to-use diluted product. The

findings of this study indicate that the optimal formulation pH range is between about 3.6 to about 4.7." (*Id.* at col. 15:23-26; *see also id.* at col. 2:20-22, 3:34-39, 4:24-31.)

A buffer has a capacity to resist changes in pH, and thus can be added as a separate and distinct component to pharmaceutical compositions in order to help the compositions maintain the optimal pH range (such as the range of "about 3.6 to about 4.7" stated in claim 1 of the '102 Patent). (Id. at col. 4:20-24, 4:49-57, 13:43-49, 27:59-67.) Indeed, the various methods of making the compositions disclosed in the patents in suit all include a step of "adding buffer" in addition to the nicardipine and the tonicity agent, pH adjuster or cosolvent to create compositions that maintain a desired pH range. (Id. at col. 8:33-64; see also id. at col. 2:28-37). All of this comports with the Examiner's statement that the reasons for allowance for the '102 Patent included that the claimed compositions have a separately added "buffer to maintain pH from about 3.6 to about 4.7." (JA Ex. J at A-188.) Because the '102 Patent is the parent or grandparent to the other patents in suit, and the patents have the same specification, the prosecution history of the '102 Patent is relevant to the other patents in suit as well. *See Ormco Corp. v. Align Tech. Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007).

3. The '405 Patent demonstrates that the "buffer" is separate and distinct.

U.S. Patent No. 5,164,405 ("the '405 Patent") further supports Exela's proposed construction that the claimed buffer is a separate and distinct component added to maintain an optimal pH range throughout the shelf life of the claimed product (*e.g.*, a pH from about 3.6 to about 4.7). The '405 Patent is incorporated by reference in the common specification (JA Ex. A at col. 1:35-38, 27:46-51) and was discussed during prosecution of the patents in suit (*e.g.*, JA Ex. G at A-141-42). The '405 Patent thus constitutes intrinsic evidence that sheds light on the meaning of the buffer limitation. *Powell v. Home Depot U.S.A., Inc.*, 663 F.3d 1221, 1231 (Fed. Cir. 2011) ("[P]rior art cited in a patent or cited in the prosecution history of the patent

constitutes intrinsic evidence." (quoting *Kumar v. Ovonic Battery Co.*, 351 F.3d 1364, 1368 (Fed. Cir. 2003); *V-Formation, Inc. v. Benetton Group SpA*, 401 F.3d 1307, 1311 (Fed. Cir. 2005) (citing same quotation). Not only is it proper to consider such intrinsic evidence in construing the meaning of a disputed claim term, not doing so constitutes reversible error. *V-Formation*, 401 F.3d at 1311 (discussing *Arthur A. Collins, Inc. v. N. Telecom Ltd.*, 216 F.3d 1042, 1044-45 (Fed. Cir. 2000), where the Federal Circuit "rejected the district court's claim construction, which 'declined to consider the teachings of [prior art referenced in the patent] to ascertain the meaning'" of a claim).

The '405 Patent discloses prior art formulations of nicardipine hydrochloride in ampules that can be diluted and reconstituted for intravenous administration to patients. (JA Ex. K at col. 1:30-44, 2:44-3:10.) It explains that a problem occurs in preparing nicardipine hydrochloride compositions if there is a "lack of pH control" during manufacturing. (Id. at col. 6:25-41.) According to the specification, nicardipine hydrochloride has poor solubility at higher pH levels, and it will precipitate out of the composition (or solution) if the pH rises during manufacturing. (Id.) "This precipitation necessitates very prolonged mixing times to completely dissolve the nicardipine and increases the potential for the manufacture of sub-potent batches if these prolonged mixing times do not result in complete dissolution of the nicardipine." (Id. at col. 6:35-40.)

"In order to overcome both the manufacturing problems and the pH changes, it was conceived [in the '405 Patent] to ***add*** a dilute buffer solution" to the nicardipine hydrochloride compositions. (*Id.* at col. 6:42-45 (emphasis added).) The addition of the separate and distinct buffer can be seen with reference to the Example B formulation from the '405 Patent, which is shown below. Example B recites the active ingredient (nicardipine HCl), tonicity adjusters

(sodium chloride and sorbitol), a pH adjuster (hydrochloric acid), and water for injection. None of these ingredients are buffers:

TABLE 1

Unsatisfactory Prior Art Formulations of Nicardipine HCl (1 mg/ml) for Injection

	Example A	Example B
Nicardipine HCL	1.0 mg	1.0 mg
Sodium Chloride	6.0	0
Sorbitol	0	50.0 mg
Hydrochloric acid	qs to pH 3.5	qs to pH 3.5
Water for Injection	qs to 1.0 ml	to 1.0 ml

(*Id.* at col. 7:33-40.) The Example B formulation was labeled "unsatisfactory" in the '405 Patent because it is subject to pH changes during autoclaving (i.e. sterilization). (*Id.*) Thus, "it was conceived to ***add*** a dilute buffer solution to the sorbitol formulation of Example B." (*Id*. at col 6:40-45.) "The amount of buffer, namely citric acid monohydrate and sodium hydroxide ***added*** (0.0025M citrate equivalent) was sufficient to maintain the pH in the range of 3.5 to 3.8 after autoclaving (Table 3) but was sufficiently dilute to be buffered by body fluids on injection." (*Id*. at col. 6:64-7:1.)

The ability of the separately-added buffer to maintain the desired pH range in the formulation enhanced the stability of the product:

> The control of pH of the formulation is also essential to maintain the aqueous solubility of the nicardipine salts to a sufficient extent that the therapeutically desirable dose strengths can be manufactured and are ***physically stable***, i.e. do not give evidence of precipitation. ***Maintenance of the necessary pH range can be best controlled by the use of a suitable buffer system***.

(*Id.* at col. 4:26-32 (emphasis added); *see also id.* at col. 4:57-62.) The '405 Patent further discusses stability testing of compositions manufactured both with and without buffers throughout Examples II-IV (encompassing Tables 1-10). Evaluating the results of these tests, the '405 Patent concludes that compositions with added buffers showed "improved

compatibility" (i.e. were more stable) as compared to compositions without buffers because the buffer maintained the pH in the desired range. (*See, e.g., id.* at col. 9:35-48; *see also id.* at col. 5:44-8:67, 10:1-32, Fig. 2.)

Therefore, whether a particular component of the formulation is or is not a buffer under the '405 Patent is directly relevant to the proper construction of the buffer limitation in claims of the patents in suit. By requiring the claimed buffer to be a separate and distinct component of the composition, Exela's proposed construction is consistent with the intrinsic record.

4. Plaintiffs' construction of the "buffer" limitations ignores the intrinsic evidence that the buffer is a separate and distinct component of the claimed pharmaceutical compositions.

Plaintiffs' proposed construction of the "buffer" limitations is consistent with Exela's proposed construction in requiring the buffer to maintain the pH within an optimal pH range. (D.I. 48-1, Ex. A at 6-7.) The disagreement between the parties is that Plaintiffs' proposed construction ignores the fact that the buffer is separate and distinct from the other components in the claimed pharmaceutical compositions. As discussed above in Sections IV.B.1-IV.B.3, the intrinsic evidence clearly explains that the buffer is separately-added to the claimed compositions and is a separate and distinct component from the other components of the compositions. Plaintiffs' proposed construction thus should be rejected by the Court because it does not clearly define the requirements of the buffer, and Exela's proposed construction based on the intrinsic evidence should be adopted.

V. CONCLUSION

For the foregoing reasons, Defendant Exela respectfully requests that the Court adopt its proposed claim constructions.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I, Benjamin J. Schladweiler, hereby certify that on February 20, 2015, a true copy of the foregoing ***Defendants' Opening Claim Construction Brief*** was served via electronic mail upon the following counsel of record:

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